8th ICLAS/CALAS Symp., Vancouver 1983 · Gustav Fischer Verlag · Stuttgart · New York · 1985

Mühlbock Memorial Lecture: Medical Advances Resulting from Animal Research*

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Most medical advances would not have been possible without basic research on animals, and many diseases that were once fatal have become treatable because of such research. I shall confine my remarks to research in the cardiovascular field, since most of my investigative endeavors have been directed toward devising surgical treatment for cardiovascular diseases which had previously resisted efforts at therapeutic resolution.

Aneurysms of the Aorta

Until several decades ago, a number of cardiovascular diseases that now have a good prognosis were considered fatal. No effective treatment was known despite many unsuccessful efforts to treat these patients. Among these conditions is aneurysm of the aorta, which has a fairly characteristic course. With time, it will rupture, and before effective treatment was developed, all patients with this disease died. Indeed, some prominent people, including Albert Einstein and Charles DeGaulle, died from a ruptured aneurysm. The operation that is done to remove an aneurysm of the abdominal aorta and replace it with an aortic homograft was performed in laboratories on animals in a number of institutions before it was performed on human beings in 1952. In our animal research laboratory, we studied this procedure for four years, beginning in 1948, to perfect the technique and to insure that it worked and that all technical problems had been solved before we tried it in man in 1952. CHARLES DUBOST, a surgeon in Paris, had also been working on this problem at the same time as we were. He actually performed this operation a few months before we did, although at that time we did not know it.

With time, we realized that the good results of our animal studies could be duplicated in man and that patients could resume normal activities after the operation. We also observed, in studies in animals and in man, that in time aneurysms developed in the homografts. We recognized that we had to find a substitute for the homograft, not only because it eventually degenerated but also because the general availability of homografts was limited, their processing was inconvenient, and they were usually not readily available in an emergency that required the removal of an aneurysm.

* Supported in part by HEW research grant HL-17269, National Heart and Blood Vessel Research and Demonstration Center, Houston, Texas.

Like many other researchers, we therefore began to search for a substitute for the homograft. This research also originated in the animal laboratory. We began studying various materials, particularly certain types of plastic materials, such as nylon, Teflon®, and Dacron®. Almost serendipitously, I went to one of the department stores in Houston to purchase some materials for this study. The only available synthetic material at the time was Dacron®, and we experimented with it first. We later were able to procure other synthetic materials, but Dacron® proved to be the best of the materials that we had studies over a period of about five years in our animal laboratory. After these extensive animal studies, we were convinced that this graft would function properly, and we were ready to use it clinically.

The first successful replacement with a Dacron® graft after resection of an aneurysm of the abdominal aorta in man was performed on September 2, 1954. The graft was made from two sheets of Dacron®, purchased from a department store and cut in the form of a Y in order to replace the terminal abdominal aorta; I sewed the edges on my wife's sewing machine. This is the way we first made tubes of Dacron® and studied them in animals.

We then began to look for a means of weaving and knitting these tubes and bifurcations. Working with Professor Thomas Edman (an expert in the engineering of weaving machines) in the experimental laboratory for about seven or eight years, we devised machines that could do this, since none were available at that time. This development eventually led to the manufacture of Dacron® knitted and woven grafts of various sizes and shapes.

Later, more experiments were done on animals. While working on the development of an artificial heart, we were trying to solve the compatibility of the interface with blood, and the use of a velour surface was suggested to us as a means of enhancing the attachment of what we call the neointima to the graft. That velour surface proved extremely successful, but unfortunately, only temporarily. We also noted from animal research that with time this material not only intimately attached itself to the neointima forming fibroendothrombi but also allowed considerable accumulation of this material. The reason is that there is no ingrowth of tissue because, in an artificial heart, the outside layer is solid and tissue cannot be introduced through it. The Dacron® graft was successful because normal tissue invaded the interstices and actually became attached to the neointima, so that it did not continue to accumulate. It did serve a useful purpose, however, in improving the Dacron® graft. We therefore added velour later to the Dacron® graft. This is an example of how one animal experiment for one purpose served to enhance another procedure for another purpose.

Our current Dacron® velour grafts are used all over the world, are readily available, and have proved highly successful. We have patients who have had this graft intact for more than twenty years, and it is still functioning well. These patients lead perfectly normal lives and certainly would have died if they had not had resection of the aneurysm and replacement with the graft.

Aneurysms of the Thoracic Aorta

After we became convinced that it was possible to resect an aneurysm of the abdominal aorta and replace it with a graft, we began to try to devise a surgical technique for aneurysms of the thoracic aorta. Experimental work was needed to determine the factors in the thoracic aorta that could affect the procedure that were not evident in the abdominal aorta. We learned that there were a number of these. For example, in the abdominal aorta, occlusion of that segment does not interfere with renal function or vascularity of the spinal cord. Thus, there were two important

complications that might develop from resecting a descending thoracic aorta that did not occur with resection of an abdominal aorta. The next problem was to find means of preventing those complications, but in the meantime, we had patients dying from ruptured aneurysms of the thoracic aorta.

When a patient with an aneurysm of the thoracic aorta first consulted us, we explained to him that there was no treatment for this huge aneurysm other than resection. We also told him that the operation had never been done on a human being, although we believed that the same techniques that we had developed in animals could be performed in man. In addition, we explained some of the complications that occur in about 2 or 3 percent of cases. Our patient was having very severe, almost uncontrollable, pain in the back, and he agreed to the operation. It fortunately proved successful, and an arteriogram made nine years later showed the graft functioning well. The patient had cancer of the lung at that time, and we resected the cancerous lobe. He did well for another six years and then died of metastatic cancer, nearly fifteen years after the original operation. One of our patients is alive thirty years after resection of a large aneurysm of the descending thoracic aorta and graft replacement.

Aneurysm of Ascending Aorta and Aortic Arch

We still had to find methods of treatment for aneurysms of the ascending aorta and the aortic arch. Our first effort to deal with these was to develop an experimental model that would allow us to determine the amount of time we could stop the circulation to the brain without permanent damage; for that purose we used hypothermia. I take this opportunity to pay tribute to one of your great Canadian surgeons, Dr. WILFRED G. BIGELOW, who was a pioneer in this field. We followed some of his contributions very closely. We discovered that hypothermia was a feasible procedure, but it did not provide enough time, and our technique was inadequate.

Heart-lung Machine

The heart-lung machine is a good example of the years of research required in the animal laboratory to perfect this machine, which was pioneered by Dr. JOHN GIBBON. One of the many problems encountered in its development was finding a suitable pump. I had been experimenting in our laboratory with a roller pump and suggested to Dr. GIBBON that it might adapt to the original machine that he had assembled some years before. Fortunately, it proved to be highly satisfactory, and it has been used ever since. After more than twenty years of research on animals, the heart-lung machine was successfully used for the first time by Dr. GIBBON on a patient in Philadelphia in 1953.

During this time, many of us were also experimenting with the heart-lung machine, and its successful application gave us the courage to proceed with its use clinically. With this machine, it was possible to bypass the ascending aorta and aortic arch so that aneurysms at these sites could be safely resected. We have had many patients who led productive lives after having this operation, and who would have died without treatment. One of our patients, an 11-year-old boy, benefitted greatly from the animal research that led to perfection of the techniques for resecting an aneurysm of both the ascending aorta and descending thoracic aorta. He is now a college student leading a perfectly normal life.

We use the heart-lung machine for resection of an aneurysm in the aortic arch, both to maintain viability as well as to control the amount of hypothermia the patient needs and to return his body to normothermia. Thus, the heart-lung machine developed in the animal laboratory has made possible another important field of cardiovascular surgery. Accordingly, most infants born with congential anomalies of the heart who previously were condemned to die within a few days to a few years can now have their cardiac abnormalities corrected and look forward to normal lives.

Thoraco-abdominal Aneurysms

In patients with thoraco-abdominal aneurysms, we often have to resect the entire descending thoracic and abdominal aorta, which means, of course, replacement of the important vessels that provide circulation to the abdominal viscera, including the iliac, superior mesenteric, and renal arteries. Again, we had to devise this technique and perfect it on animals before applying it to human beings. Its successful application to man is exemplified by a patient who was still living more than twenty years after the operation.

Dissecting Aneurysms

A somewhat different type of aneurysm is the dissecting aneurysm. It is different in that it separates the wall of the aorta, and it is far more deadly than the other aneurysms that I discussed earlier. Fifty percent of these patients will die within a few days after onset of symptoms, that is, the development of the dissecting process. Ninety percent will be dead within three months. Rarely does a patient with this type of aneurysm survive a year without treatment. There was no treatment for dissecting aneurysms until 1954, when we first successfully treated a patient with a dissecting aneurysm of the descending thoracic aorta. This again was a technique that we devised from our animal studies.

We have just completed an analysis of twenty-eight years' experience with surgical treatment of dissecting aneurysms of the aorta. The analysis showed that surgical treatment favorably alters the highly fatal natural course of this disease. In our series, 57 percent survived five years; 32 percent, ten years; and 5 percent, twenty years, whereas in a comparable series of nonsurgically treated patients, only a few survived one year, and none lived longer than three years.

Coronary Disease

Interest in the treatment of coronary disease goes back a long way, although there was no effective surgical method to restore circulation to the distal arterial bed until relatively recently. In the late 1950s and early 60s, surgeons studied this problem intensively in the laboratory. The techniques that were available at that time were endarterectomy, a procedure that had been developed for occlusive disease by dos Santos in Portugal, and the bypass principle, which was a procedure developed by Kunlin in France. I had the great privilege and pleasure to work with

both of these men when I was «l'assistante d'étrangé» in the Leriche Clinic at the University of Strasbourg.

We also developed the patch-graft principle in the laboratory to widen the lumen of a compromised arterial wall by supplementing it with a graft. A combination of endarterectomy and angioplasty seemed to be the logical procedure for a well-localized occlusive process. These were the first procedures used in human beings after many experiments in animals.

One of our patients with occlusion of the left anterior descending and the left coronary arteries who was operated on nineteen years ago is still living. I see him every year for a checkup, and three months ago when I examined him, he was still asymptomatic. I cannot explain why he has had virtually no progression of the disease, because some progression occurs in most patients with arteriosclerosis.

Like others, we were still experimenting in the laboratory with methods of restoring circulation to the coronary arterial bed beyond the occlusive process. One of your great pioneers in cardiovascular surgery, Dr. GORDON MURRAY, had shown in animals that he could use a segment of the artery from the subclavian, for example, as we do in the blue baby operation, to improve circulation in the coronary arterial bed distally. Because we thought that this was a much more difficult operation, we began experimenting with a procedure called aortocoronary bypass; it consists in attaching a graft to the ascending aorta which, of course, is the site of origin of the coronary arteries, and then attaching it to the distal coronary arterial tree beyond the occlusive lesion, depending on which vessel (right, left, anterior, descending, or circumflex) is involved.

The procedure we performed on animals was published in *Circulation* in 1961. For about five years, we persisted in our experimental work in animals improving our technique in our effort to perfect it and reduce the risks of the operation in every possible way.

After this long experimental period, we decided to apply the aortocoronary bypass that we had been doing in the animal laboratory all this time to man, keeping in mind at that time that we had about a 50 percent success rate, and over the next several years, had increased it to about 80 percent. We therefore were reasonably confident that we could apply it safely and successfully to human beings. Although we had not planned to perform this operation on our patient at that moment, we believed that it was the only procedure left for us to do if we were going to save his life. So we did just that. We performed aortocoronary bypass, and fortunately, it proved very successful. The patient recovered completely without incident, and in ten days, was out of the hospital. We kept in close contact with him after the operation, and seven years later, we asked him if we could do arteriography, even though he had no symptoms. He agreed to have the procedure, which showed the graft still functioning well. That case initiated the clinical application of aortocoronary bypass. In many institutions throughout the country, it has become a fairly standard procedure. Many technical improvements have been made in preservation of the heart during the operation. In our experience, at least one or more of these grafts will be functioning in more than 90 percent of the patients after ten years.

Analysis of well over 2,000 cases of patients we have followed for more than ten years showed that among those younger than 65 years of age (we tried to get patients who had not retired), 57 percent were working full time at the end of ten years. Not only have these patients' lives been prolonged, but the annual attrition rate after this operation is less than half that of the patients with comparable disease who were not operated on. Thus, many of these patients have been returned to economic stability.

One of the main causes of death in patients with aneurysms who are operated on is coronary occlusive disease. One of our patients, for example, had severe coronary disease, an aneurysm that was about to rupture, and a lesion of the carotid artery that could cause a stroke at any time.

All these conditions can be corrected surgically, and these procedures were done on this patient in one stage. More than ten years later, the patient is well. All these techniques are the result of animal research.

Valvular Heart Disease

There was no satisfactory from of treatment for valvular heart diesease until the late 50s or early 60s. Dr. A. STARR was one of the great ioneers in this field. At a very early period, he developed the ball valve to put into the sub-coronary position.

Further animal experimentation with additional types of valves has resulted in perfecting the procedure of valvular replacement. No surgeon would consider putting a valve in a human being before it had been tested properly in animals.

One of the disappointments encountered with some of the earlier valves was the fact that the plastic materials used in some valves deteriorated with time. Deterioration in the plastic occluder results in ribbing in the valve and, with time, serious heart problems develop necessitating replacement of the valve.

One of the important developments in heart-valve research has been use of pyrolite carbon. I had the great pleasure of working with Dr. JACK C. BOKROS, who developed the first application of pyrolite carbon for valves. One of the first types of valve for this purpose was a typical ball valve, but he used pyrolite carbon as a means of developing the occluder and seating. It has been shown both in animal and in human studies that this valve does not deteriorate, and this pyrolite carbon is used in almost all valves today. This is yet another example of the importance of animal research in the development of a method that has proved of great use in combatting human disease. We have patients in whom cardiac prosthetic valves are functioning well after twenty years. That is not to say, however, that we have solved all the valve problems, as we have not. Certain complications still occur. The ideal valve is yet to be developed.

Artificial Heart/Assisted Cardiac Circulation

In the late 50s and early 60s the concept of using a pump that duplicated the function of the heart, in much the same fashion as the heart-lung machine was used to support the heart temporarily, and perhaps to replace the heart, began to be considered by experimental workers in the field and in a number of institutions including our own. We began developing pumps of various kinds, including the roller pump. We fashioned a number of different types of pumps over a period of years to pump blood and duplicate the function of the left ventricle.

As time went on, it became increasingly apparent that total replacement of the heart was going to be an extremely complicated problem, and it still is. It was through animal experimentation that we began to realize that we could support a certain amount of the load of the cardiac output with this pump, so that if the heart was pumping only two litres a minute, we could add another two or three litres with this supplementary pump. We were able to put this pump just outside the chest of a calf, and it performed this function. We obviously had to perform a long series of experiments to perfect the procedure. As time went on, we found that there were problems that we could solve, but others that we could not solve. One of our biggest problems was

thromboembolism, which we partially solved with the use of Dacron® velour on the surface. This worked well for ten days to two weeks but, beyond that time, layering accumulated and interfered with the function of the pump. Fortunately, most patients in whom this pump could be used did not require more than a week to ten days of cardiac support, before the heart could resume pumping on its own.

We first applied this concept in patients who could not be weaned off the heart-lung machine. These patients, on whom a corrective procedure had been done, had severe heart disease, but their hearts were so badly damaged that they could not take over after the operation. We decided to try the pump first in these desperate cases. The pump was attached by one tube to the left atrium to bring oxygenated blood into the pump and another tube to return th blood to the arterial system to one of the major arteries (femoral, axillary, or ascending aorta).

In the first patient in whom we applied this technique successfully, it was possible to wean the patient off the heart-lung machine following resection and replacement of the aortic and mitral valves, with the pump flowing 3,000 ml/min. By the morning of the fourth day after operation, the pump flow rate was gradually reduced to 400 ml/min. At noon on that day, the systemic blood pressure progressively decreased, and the left atrial pressure increased moderately and was associated with decreased urinary output to about 10 ml/30 min. The rate of the left ventricular bypass pump was then increased from 400 ml/min to 800 ml/min, with immediate diuresis and restoration of left atrial pressure to normal. On the seventh day after operation, an infusion of 500 ml of saline solution was given during renal function studies, after which left atrial pressure slowly rose during an interval of six hours. Acute pulmonry edema rapidly developed. Left atrial pressure rose sharply to 45 mm Hg; at this time the outflow of the left ventricular bypass pump was increased from 450 to 1,400 ml/min. Within minutes the left atrial pressure dropped rapidly to about 15 mmHg, and all signs of acute pulmonary edema disappeared. The patient's condition continued to improve, and on the ninth day after operation the outflow of the pump was reduced to 350 ml/min. Continued reduction in output of the pump caused no rise in left atrial pressure, and on the tenth postoperative day, use of the pump was discontinued. After six hours no increase in left atrial pressure occurred, and the pump was removed. The patient left the hospital on the twenty-ninth day after operation and later returned to work and resumed normal activities, but about six years later, was tragically killed in an automobile accident. We were able to obtain the heart; the valves were functioning well, and the sites at which the tubes were attached looked perfectly normal in every way. This successful case confirms the value of cardiac assistors, which are now being used in most medical centers. There are several different methods of temporary cardiac assistance, the most common of which is the intra-aortic balloon.

This experience also provided a means of studying total cardiac replacement by two ventricles. Like others, we were interested in the use of total heart replacement and did a number of experiments, mostly in calves, using the two ventricles after as much of the heart was removed as is done for a heart transplant, and the artificial heart was applied. There are a number of problems associated with their use, and they occur in animals in spite of erverything we have done to try to prevent them. A great deal more laboratory research is needed in this area. As far as using the artificial heart as a temporary measure, however, in much the same way as we use the left ventricular assistor, it may have possibilities to maintain the viability of the patient for short periods, since most of the complications do not occur early, but develop over periods of extended time. It may well be that in some patients, who are dying on the operating table, as was the patient on whom we used the left ventricular assistor, we can, with the artificial heart, maintain viability in the patient's ventricles while waiting for a donor heart to become available for a heart transplant.

Conclusion

Those individuals and groups who try to deter the use of animals for scientific research, I believe, do so with a certain degree of sincerity, and they have compassion for the humane care of animals, but I am sure that they do not appreciate or understand the way that scientists work with animals. In most research laboratories throughout the world, scientists who work with animals are just as compassionate and have just as much humane concern as any of those who crusade for the humane care of animals. I also believe that they do not appreciate the fact that while they speak of alternative methods of replacing animal research, they obviously do not realize that in certain types of scientific research, as I have described, there are no alternative methods to animals other than man. Most of the advances I have told you about today in the cardiovascular field have been achieved by using animals for research. These could not have been done by any other method. There is no alternative way to establish whether a Dacron® graft or the heart-lung machine works except by using them in animals, or by replacing that animal with man. I do not believe that our society is ready to apply an experimental procedure to man that has not been tested in every possible way in another mammal.

The efforts of some to insure humane treatment of animals in the research laboratory disregard the existing rules and regulations that govern their use in scientific research. I was so pleased to hear the representative of government here say that self-regulation is the better method. In my opinion, it is the best method and should be the one that we want to use. It has worked. Not only are there existing guidelines for the use of animals in research by governmental funding agencies, but there are also guidelines and even regulations within the research institutions themselves. We cannot, in our institution, do any kind of research without having it approved by the research committee composed of our peers and persons who represent the community. The research must be approved, even though the funds might be available for that research, before the study can be initiated. We, like other institutions, also have an animal research committee that is responsible for the proper care of animals. We have developed our methods by selecting the best methods from other institutions. Those concerned about animal research also seem to disregard the great advances that have been made through animal research, some of which I have exemplified, that have made it possible for literally millions of people to be relieved of suffering and premature death and to be restored to a normal life.

Finally, those scientists, veterinarians, physicians, surgeons, and others who do research in animal laboratories are as much concerned about the care of the animals as anyone can possibly be. Most of them have humanitarian characteristics – concern for the dignity of life and compassion for animals – because they have an important bearing on the quality of the research that they do. If those who oppose animal research could understand this, they would not use the sensationalism, teasingly brought out as abuses, as evidence of what goes on in most laboratories in this country. This simply is not true.

The fact that abuses sometimes occur should not obliterate the compassion for, and proper care of, animals in the laboratories of most institutions where scientific advances are being achieved. One cannot completely eliminate unethical and nonhumanitarian elements in our society. Certainly, this has not been done in other areas, such as crime, violence, and drug abuse. We have not been able to eliminate these in spite of severe governmental regulations. We try to reduce them and try to educate people to understand them. Indeed, these deplorable characteristics fortunately are centered in a small core of our society.